c) outputting said quantified association to a suitable output hardware.

36. (Amended) The method according to claim 32, wherein said molecule or molecular complex comprises amino acids 1-514 of IMPDH, oxidized inosine monophosphate thioimidate intermediate ("XMP*"), and mycophenolic acid ("MPA").

REMARKS

In response to the Examiner's objection, applicants have amended the title to delete reference to subject matter not claimed in the present application. Support for this amendment appears, e.g., in the specification as filed at page 1, lines 18-22.

Applicants have amended the specification to recite the priority information claimed in this application.

In response to the Office Action, applicants have canceled claims 24-25 without prejudice. The cancellation of this subject matter is without waiver of applicants' rights to file divisional or continuing applications directed to the cancelled subject matter and claiming priority from this application.

Applicants have amended claims 23 and 36 in response to the Examiner's rejections (see below). Specifically, applicants have amended claims 23 and 36 to recite Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH"), mycophenolic acid ("MPA") and oxidized inosine monophosphate thioimidate intermediate ("XMP*") at the first occurrence. Support for this amendment appears throughout the specification as

filed, e.g., at page 10 lines 4-5 (IMPDH), line 7 (MPA) and page 10, lines 6 and page 10, line 33 to page 11, line 1 (XMP*).

Applicants have amended claims 23 and 29 to recite an outputting step. Support for this amendment appears throughout the specification as filed, e.g., at page 24, lines 13 to 32 and page 29, lines 7-20. Applicants have further amended claims 23 and 29 for clarity.

None of these amendments add new matter. Claims 23 and 27-36 are now pending.

The Objections

Restriction Requirement

In response to the Restriction Requirement, applicants have cancelled claims 24-25.

Title

The Examiner has objected to the title as not indicative of the invention to which the claims are directed. Applicants have obviated the Examiner's objection by amending the title of the present application to recite "METHODS OF USING THE STRUCTURE COORDINATES OF MOLECULES COMPRISING AN IMPDH-LIKE BINDING POCKET".

Priority Claim

The Examiner states that specific reference to the earlier filed application must be made in order to claim priority under 35 U.S.C. § 120. Applicants have amended the specification to recite the priority information claimed in the instant application.

Disclosure

The Examiner has objected to claims 23 and 29 as containing improper periods within the claims. Applicants have obviated this objection by amending the claims to recite "a)" and "b)" rather than "a." and "b." as suggested by the Examiner.

The Rejections

35 U.S.C. § 101

Claims 23 and 27-36 stand rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Specifically, the Examiner contends that claims 23 and 27-36 recite only steps of computation and analysis and are mathematical operations that do not recite any concrete or tangible results. The Examiner further contends that claims 23 and 27-36 are not supported by either specific or substantial utility or a well established utility. The Examiner contends that "[t]he instant claims do not recite any specific result, nor any actual transformation of data, which would produce a result that is concrete, tangible and useful." In light of the claim amendments, applicants traverse.

Applicants have amended independent claims 23 and 29 to recite the additional step of "outputting said quantified association to a suitable output hardware." Output hardware may include, for example, a graphical display terminal, a printer, or a disk drive (see, e.g., specification page 24, lines 15-21). As amended, the methods of claims 23

and 29 recite a useful, concrete, and tangible result, and are therefore directed to statutory subject matter under Section 101 as discussed in more detail below.

To support his contentions, the Examiner cites In re Warmerdam and Schrader for the proposition that "[a] process that consists solely of the manipulation of an abstract idea is not concrete or tangible." In re Warmerdam states simply that "the dispositive issue for assessing compliance with Section 101 in this case is whether the claim is for a process that goes beyond simply manipulating 'abstract ideas' or 'natural phenomena'." In re Warmerdam, 31 USPQ2d 1754, 1759 (1994). In re Schrader describes the so-called Freeman-Walter-Abele test as the standard for patentability of a claim reading on a mathematical algorithm. In re Schrader, 30 USPQ2d 1455, 1457 (1994). In re Warmerdam also relies on the Freeman-Walter-Abele test. In re Warmerdam, 31 USPQ2d at 1757-58.

The Examiner further cites Parker v. Flook, In re Gelnovatch, In re de Castelet, and In re Abele, cases purported to involve claimed processes that do not achieve a practical application. In Flook, the Supreme Court held that a method of updating alarm limits was unpatentable because "[t]he only difference between the conventional methods of changing alarm limits and that described in respondent's applications rests in ... the mathematical algorithm." Parker v. Flook, 198 USPQ 193, 195 (1978). However, the Supreme Court later clarified that Flook "did no more than confirm the 'long-established principle' that laws of nature, natural phenomena, and abstract ideas are excluded from patent protection." AT&T, 172 F.3d at 1356 (discussing Diamond v. Diehr, 450 U.S. 175, 185 (1981)).

Similarly, in In re Gelnovatch, the CCPA held that a process for determining a set of values for use in a mathematical model of an electronic circuit was unpatentable because it "merely perform[s] a series of mathematical calculations." In re Gelnovatch, 201 USPQ 136, 145 (1979). In In re de Castelet, a method of generating a curve or family of curves was held to be drawn to nonstatutory subject matter because it recites "a process for solving a set of mathematical equations per se." In re de Castelet, 195 USPQ 439, 446 (1977). These cases simply confirm that "claims merely reciting methods of calculation" are nonstatutory. In re Gelnovatch, 201 USPQ at 143.

The Examiner also cites In re Abele, wherein claims directed to producing an improved X-ray image were held to be nonstatutory because "apart from the mathematical calculations, the remaining steps were well known." In re Abele, 214 USPQ 682, 684 (1982). However, after State Street, "the Freeman-Walter-Abele test has little, if any, applicability to determining the presence of statutory subject matter." State Street Bank &Trust Co. v. Signature Financial Group, Inc., 149 F.3d 1368, 1374 (1998).

Consequently, it is not clear that any of In re Warmerdam, In re Schrader, Flook, In re Gelnovatch, In re de Castelet, or In re Abele most accurately reflect the current interpretation of what constitutes statutory subject matter under section 101 in light of State Street, discussed in more detail below. In particular, both In re Warmerdam and In re Schrader rely on the so-called Freeman-Walter-Abele test explicitly set aside in State Street. According to current PTO practice, "[o]ffice personnel should no longer rely on the Freeman-Walter-Abele test to determine whether a claimed invention is directed to statutory subject matter." MPEP § 2106 I.

Each of In re Warmerdam, In re Schrader, Flook, In re Gelnovatch, In re de Castelet, and In re Abele was decided before the Federal Circuit reexamined the standards governing patentability of "the process of manipulation of numbers" in the landmark State Street case. See AT&T Corp v. Excel Communications, Inc., 172 F.3d 1352, 1356 (1999). More recent case law and Patent Office practice have emphasized that the requirements of section 101 are satisfied where method claims that include mathematical manipulations produce a useful, concrete, and tangible result, rather than a mere "mathematical abstraction." See AT&T, 172 F.3d at 1359. Accordingly, claims resulting in a signal useful for billing purposes (AT&T, 172 F.3d at 1352), a share price (State Street, 149 F.3d at 1368), a smooth waveform (In re Alappat, 31 USPQ2d 1545 (1994)), or a number (Arrhythmia Research Technology Inc. v. Corazonix Corp., 22 USPQ2d 1033 (1992)) are regarded as statutory subject matter.

In particular, as noted by the court in State Street, "[t]he question of whether a claim encompasses statutory subject matter" focuses on the practical utility of the subject matter. State Street, 149 F.3d at 1375. Where the claim produces a useful, concrete, and tangible result, the claim is directed to statutory subject matter, "even if the useful result is expressed in numbers." See id. Further, "the mere fact that a claimed invention involves inputting numbers, calculating numbers, outputting numbers, and storing numbers, in and of itself, would not render it nonstatutory subject matter." Id. at 1374. After State Street, a section 101 inquiry "focuses on whether the mathematical algorithm is applied in a practical manner to produce a useful result." AT&T, 172 F.3d at 1360. In fact, according to the MPEP, "[o]nly when the claim is devoid of any limitation to a practical application in the technological arts should it be rejected under [section 101]." MPEP § 2106 II.A.

Moreover, under this standard, there is no absolute requirement for a transformation of data step, as the Examiner contends. In particular, a physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application." AT&T, 172 F.3d at 1358.

Applicants' claims produce a useful, concrete, and tangible result, namely, a quantified association between a chemical entity and an IMPDH-like binding pocket. This result is not merely "the manipulation of an abstract idea," as the Examiner contends. The quantified association obtained from applicants' claimed processes is analogous to the share price obtained in State Street and to the signal useful for billing purposes in AT&T. Just as the State Street share price is useful to facilitate share trading (State Street, 149 F.3d at 1373), and the AT&T signal is useful to facilitate differential billing (AT&T, 172 F.3d at 1358), applicants' quantified association is useful to facilitate the process of drug discovery and differentiate various chemical entities based on the quantified association. Applicants' claims allow the calculation of binding affinities for IMPDH-like binding pockets. Indeed, applicants' quantified association has a specific, substantial, credible, and well-established utility, e.g., for the design, selection, and synthesis of chemical entities, including inhibitory compounds, capable of binding to IMPDH-like binding pockets. See, e.g., specification page 11, lines 23-28. In short, applicants' result is just as useful, concrete, and tangible as the results obtained in State Street and AT&T. See also MPEP § 2106 II.B. ("Only when the claim is devoid of any limitation to a practical application in the technological arts should it be rejected under 35 U.S.C. 101.").

Accordingly, applicants' claims are directed to statutory subject matter under section 101. Applicants therefore request that the Examiner withdraw these rejections.

35 U.S.C. § 112, first paragraph

Claims 23 and 27-36 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Specifically, the Examiner contends that because the claimed invention is not supported by either a specific and substantial utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants traverse.

For the reasons set forth above, applicants' claimed invention is supported by a specific, substantial, or well established utility, namely, for the design, selection, and synthesis of chemical entities, including inhibitory compounds, capable of binding to IMPDH-like binding pockets. Accordingly, one skilled in the art would know how to use the claimed invention. To the extent that the Examiner's enablement rejection might have been based on an alleged lack of utility, applicants assert that the amendments overcome this rejection. Applicants therefore request that the Examiner withdraw this section 112, first paragraph rejection.

35 U.S.C. § 112, second paragraph

Claims 23 and 27-36 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants address each of the Examiner's specific contentions below.

i. The Examiner contends that the phrase "evaluating the ability" in claims 23 and 29 is unclear because it implies that the ability is chosen by some kind of

criteria. The Examiner states however that "[a]pplicant can resolve this issue by particularly pointing out what type of the evaluation relating to the ability of a chemical entities are chosen." Applicants traverse the Examiner's contention that the phrase is unclear.

Claims 23 and 29 recite a method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex. Accordingly, the relevant criterion to be applied is this association. Further, as set forth throughout the specification as filed, "associating with" refers to a condition of proximity between a chemical entity or compound, or portions thereof, and an IMDPH molecule or portions thereof. The association may be non-covalent – wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions – or it may be covalent. See, e.g., specification page 13, lines 17-23. To the extent that the Examiner's rejections might have been based on the Examiner's additional contention that the phrase "computational means" is indefinite, applicants assert that the claim amendments overcome this rejection. Applicants therefore request that the Examiner withdraw this aspect of the rejections.

ii. The Examiner contends that the phrase "quantify the association" in claims 23 and 29 is unclear because it implies that the determined quantity is chosen by some kind of criteria. The Examiner states however that "[a]pplicant can resolve this issue by particularly pointing out what kind of criteria for [sic] quantity relating to the ability of a chemical entity to associate with a molecule or molecular complex, is chosen." Applicants traverse the Examiner's contention that the phrase is unclear.

As set forth throughout the specification as filed, "associating with" refers to a condition of proximity between a chemical entity or compound, or portions thereof, and an IMDPH molecule or portions thereof. The association may be non-covalent – wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions – or it may be covalent. See, e.g., specification page 13, lines 17-23. Accordingly, applicants' specification sets forth the criteria for quantifying the association. Applicants therefore request that the Examiner withdraw this aspect of the rejections.

iii. The Examiner contends that the phrase "computational means" in claims 23 and 29 is indefinite because the phrase is used "without any means determination whatsoever." The Examiner further contends that "since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass." Applicants traverse.

Applicants disagree that claims 23 and 29 recite a use without active, positive steps. Specifically, claims 23 and 29 recite the active, positive steps of: employing computational means to perform a fitting operation, analyzing the results of said fitting operation to quantify the association, and outputting said quantified association.

Nonetheless, in order to expedite prosecution, applicants have amended step a) of claims 23 and 29 to clarify that the computational means employed in that step utilize the structure coordinates of IMPDH amino acids recited in that claim. Applicants assert that the claim amendments overcome this rejection, notwithstanding the traversal. Applicants therefore request that the Examiner withdraw this aspect of the rejections.

iv. The Examiner contends that claims 23 and 27-36 are indefinite because they recite abbreviations such as IMPDH, XMP*, and MPA. The Examiner states that "[a]pplicants should provide the full name." Applicants have amended the claims according to the Examiner's recommendation, thereby obviating the rejection.

Specifically, applicants have amended claim 23 to recite "Chinese hamster type II inosine-5'-monophosphate dehydrogenase ("IMPDH")" at the first occurrence. Applicants have amended claim 36 to recite "oxidized inosine monophosphate thioimidate intermediate ("XMP*")" and "mycophenolic acid ("MPA")" at the first occurrence. Applicants therefore request that the Examiner withdraw this aspect of the rejections.

Conclusion

Applicants request that the Examiner enter the foregoing amendments and remarks and allow the pending claims to issue. If the Examiner believes that a telephonic interview would be helpful, he is invited to call applicants' attorney or agents at any time.

Respectfully submitted,

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Exhibit 1

Appendix of Specification Amendments

The title:

METHODS OF USING THE STRUCTURE COORDINATES OF MOLECULES COMPRISING AN IMPDH-LIKE BINDING POCKET [AND ENCODED DATA STORAGE MEDIUM CAPABLE OF GRAPHICALLY DISPLAYING THEM]

The first paragraph, directly following the title:

This application is a divisional of United States Application 08/640,164, filed April 30, 1996, now United States Patent 6,128,582.

Exhibit 2

Appendix of Claim Amendments

23. (Twice Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex comprising all or any part of a binding pocket defined by structure coordinates of [IMPDH] Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 68, 69, 93, 273, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 330, 331, 332, 333, 334, 337, 339, 340, 364, 413, 414, 415, 416, 420, 439, 440, 441, 442, 469, and 470 according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

[a.] a) employing computational means, which utilize said structure coordinates, to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; [and]

[b.] b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket; and

c) outputting said quantified association to a suitable output hardware.

29. (Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex comprising all or any parts of a binding pocket defined by structure coordinates of IMPDH amino acids 67, 68,

69, 70, 73, 274, 275, 276, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 440, 441, 442, 443, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

[a.] a) employing computational means, which utilize said structure coordinates, to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; [and]

[b.] b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket; and

c) outputting said quantified association to a suitable output hardware.

36. (Amended) The method according to claim 32, wherein said molecule or molecular complex comprises amino acids 1-514 of IMPDH, [XMP*] oxidized inosine monophosphate thioimidate intermediate ("XMP*"), and [MPA] mycophenolic acid ("MPA").